REMARKS

The Invention

The present invention is directed to methods of treating a neoplasia in a mammal involving administering to the mammal a serum-stable nucleic acid-lipid particle comprising a nucleic acid portion that is fully encapsulated within the lipid portion. Administration of the nucleic acid-lipid particle is by injection at a site distal to the neoplasia in the mammal. In some embodiments, the lipid portion of the nucleic acid-lipid particle comprises a cationic lipid and a neutral lipid. In some embodiments, a prodrug is also administered to the mammal. In other embodiments, a chemotherapeutic agent is also administered to the mammal. In some embodiments, the administration is intravenous.

Status of the Claims

Applicants wish to thank Examiner Zara for extending the courtesy of the telephonic interview held on February 25, 2003 with Applicants' representatives Carol Fang and Eugenia Garrett-Wackowski and the subsequent telephonic conference held on February 27, 2003 with Applicants' representative Carol Fang. During these interviews, a number of issues were clarified which have helped Applicants to more fully address the concerns of the Examiner. Applicants thank Examiner Zara for her time.

After entry of this amendment, claims 1-61 are pending. Claims 1-28 and 35-46 stand rejected under 35 U.S.C. §112, first paragraph as allegedly lacking enablement; claim 6 stands rejected under 35 U.S.C. §112, first paragraph as allegedly lacking adequate written description; claims 4, 6, and 7 stand rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite; claims 1-4, 8, 10-12, 16-18, 23, 28, 39-42, 44, and 46 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated. These rejections are addressed below.

Claims 4 and 6 have been amended for clarity. New claims 48-61 have been added. Support for new claims 48-61 is found throughout the specification and

claims as originally filed (*see, e.g.*, page 20, lines 9-11 and claims 6, 8 and 9). Thus, no new matter is added by these amendments.

A version of the claims with markings to show changes to the claims are provided in Appendix A. All of the pending claims are provided in Appendix B for the Examiner's convenience.

Rejections Under 35 U.S.C. §112, first paragraph

1. Enablement

The Examiner initially maintained the rejection of claims 1-28 under 35 U.S.C. §112, first paragraph as allegedly lacking enablement.

As previously explained, a particular claim is enabled by the disclosure in an application if the disclosure, at the time of filing, contains sufficient information so as to enable one of skill in the art to make and use the claimed invention without ***undue*** experimentation. *See, e.g., In re Wands*, 8 USPQ2d, 1400 (Fed. Cir. 1988), or MPEP §2164.01. It is important to note that the possibility that some experimentation, even if such experimentation is complex or extensive, may be required for the practice of the invention does not necessarily mean that the invention is not enabled:

> The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *See*, MPEP § 2164.01.
>
> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. MPEP § 2164.06, citing *In re Wands*, 8 USPQ2d, 1400 (Fed. Cir. 1988).
>
> As MPEP § 2164.02 states, "[a] rigorous or an invariable exact correlation is not required" between a particular model and a specific condition.

> As set forth in MPEP § 2164.08, a rejection for undue breadth is inappropriate where "one of skill could readily determine any one of the claimed embodiments."

During the interview, Applicants discussed several aspects of the rejection with the Examiner. For example, it was pointed out to the Examiner that the specification provides (1) teachings regarding therapeutic nucleic acids; (2) teachings regarding preparation and properties of lipid-nucleic acid particles; (3) teachings regarding neoplasias suitable for treatment using the lipid-nucleic acid particles of the present invention; and (4) teachings regarding administration of lipid-nucleic acid particles (*see, e.g.*, page 10, line 14 to page 14, line 24; page 14, line 25 to page 18, line 31; page 19, line 28, to page 20, line 16; and page 21, lines 20 to page 22, lines 27). Moreover, as discussed with the Examiner, the teachings in the specification are affirmed by the Declaration of Dr. Ian MacLachlan, originally submitted on March 8, 2002 in response to the Final Office Action mailed October 10, 2001.

During the interview and in the Office Action mailed October 2, 2002, the Exmainer acknowledged that Applicants have provided numerous examples of *in vitro* and *in vivo* gene delivery to cells and tumors. In addition, the Examiner acknowledged that Applicants have provided numerous examples of successful tumor reduction by administration of lipid-nucleic acid particles using the presently claimed methods. However, the Examiner maintains the rejection that undue experimentation is required to enable treatment of any neoplasia in an animal. Applicants respectfully traverse this rejection.

As discussed during the interview and acknowledged by the Examiner, Applicants have demonstrated that distal administration of the nucleic acid-lipid particles of the claimed invention can be used to treat multiple types of neoplasia with multiple classes of nucleic acids (Declaration ¶8 and ¶12). For example, as discussed during the interview, the specification and declaration of Dr. MacLachlan contain multiple working examples demonstrating effective *in vivo* treatment of diverse neoplasias such as melanoma, sarcoma, fibrosarcoma, and colorectal tumors with multiple classes of nucleic

acids encapsulated in the lipid-nucleic acid particles of the claimed invention. Specifically, the additional experiments unequivocally demonstrate that diverse classes of nucleic acids encoding cytokines (*e.g.*, IL-12), tumor suppressor proteins (*e.g.*, apoptin), and bacterial toxins (*e.g.*, *Pseudomonas* exotoxin) encapsulated in the lipid-nucleic acid particles of the invention effectively inhibit growth of diverse neoplasias such as sarcoma and colon carcinoma (s*ee,* Declaration ¶7, ¶8, and ¶12). Applicants also pointed out the working examples in the specification which showed that growth of melanoma, fibrosarcoma, and colorectal tumors was inhibited by distal administration of nucleic acids encoding the suicide gene HSV-TK encapsulated in the lipid-nucleic acid particles of the present invention (*see,* Declaration ¶8). The Examiner agreed that all of these data were persuasive in demonstrating that the claimed methods of administering serum-stable lipid-nucleic acid particles can inhibit tumor growth and are effective for treating neoplasias.

Applicants also noted that further *in vitro* experiments demonstrating that multiple suicide enzymes (purine nucleoside phosphorylase and cytosine deaminase) are effective in inhibiting tumor cell proliferation (*see*, Declaration ¶12). As discussed during the telephonic interview of February 27, 2003, the Examiner agreed that the experiments persuasively demonstrated inhibition of tumor cell growth. In particular, the Examiner agreed that the experiments were persuasive in supporting claims directed to methods of treating neoplasia by administering lipid-nucleic acid particles, wherein the nucleic acids encode suicide enzymes.

Thus, as discussed in detail above, in addition to enabling claims directed to methods of treating diverse classes of neoplasias by administering lipid-nucleic acid particles, wherein the nucleic acids encode suicide enzymes, the specification also enables claims directed to methods of treating diverse classes of neoplasias by administering lipid-nucleic acid particles, wherein the nucleic acids encode diverse classes of nucleic acids, including nucleic acids encoding cytokines, tumor suppressor proteins, and bacterial toxins. Therefore, a skilled artisan, using the teachings of the

specification either alone or together with what is known to those of skill in the art, would be able to practice the invention as claimed, ***without*** undue experimentation.

In view of the foregoing remarks, Applicants assert that claims are fully enabled by the specification as originally filed.

2. Written Description

Claim 6 stands rejected under 35 U.S.C. § 112, first paragraph as allegedly lacking adequate written description. In particular, the Examiner alleges that the specification contains inadequate written description for the recitation "analogs thereof." To expedite prosecution, claim 6 has been amended to delete the recitation. Accordingly, Applicants respectfully request withdrawal of this rejection.

In view of the foregoing, Applicants respectfully request that the rejections under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejections Under 35 U.S.C. §112, second paragraph

Claims 4, 6, and 7 are rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection.

As set forth in MPEP § 2173.02, "[d]efiniteness of claim language, must be analyzed in light of (A) content of the application; (B) the teachings of the prior art; and (C) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made."

In the instant case, the specification adequately defines the terms or the terms are adequately understood to one of skill in the art, such that the claims are not indefinite under 35 U.S.C. §112, second paragraph. Several bases of indefiniteness were raised, and they will be discussed in turn.

1. Claim 4

Claim 4 has been rejected because the recitation "gene is exogenous" is allegedly unclear. Claim 4 has been amended to recite "gene is heterologous." As explicitly stated in the specification at page 12, lines 30-31, nucleic acids that are useful in the methods of the present invention can be heterologous or homologous with patient DNA. Thus, one of skill in the art would understand that a gene that is heterologous refers to a gene that is heterologous to a gene in the mammal to whom the lipid-nucleic acid particle is administered. Accordingly, Applicants respectfully request withdrawal of this rejection.

2. Claim 6

Claim 6 has been rejected because the recitation "analogs thereof" is allegedly unclear. To expedite prosecution, claim 6 has been amended to delete the recitation. Accordingly, Applicants respectfully request withdrawal of this rejection.

3. Claim 7

Claim 7 has been rejected because the recitation "gene is homologous" is allegedly unclear. As explicitly stated in the specification at page 12, lines 30-31, nucleic acids that are useful in the methods of the present invention can be heterologous or homologous with patient DNA. Thus, one of skill in the art would understand that a gene that is homologous refers to a gene that is homologous to a gene in the mammal to whom the lipid-nucleic acid particle is administered. Accordingly, Applicants respectfully request withdrawal of this rejection.

Rejections Under 35 U.S.C. § 102(e)

Claims 1-4, 8, 10-12, 16-18, 23, 28, 42, 44, and 46 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Kirn *et al.* (U.S. Patent No. 6,133,243). Claims 1-4, 8, 10-12, 16-18, 23, 28, 39-42, 44, and 46 are also rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Hung *et al.* (U.S. Patent No. 6,197,754). Each of these rejections is addressed in turn below, in the order raised by the Examiner.

For a rejection of claims under § 102(e) to be properly founded, the Examiner must establish that a single prior art reference discloses each and every element of the claimed invention. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). In *Scripps Clinic & Research Found. v. Genentech, Inc.*, 18 U.S.P.Q.2d 1001 (Fed. Cir. 1991), the Federal Circuit held:

> [A]nticipation requires that all of the elements and limitations of the claim are found with a single prior art reference. . . .There must be ***no difference*** between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention.

Id. at 1010 (emphasis added). Anticipation can be found, therefore, only when a cited reference discloses ***all*** of the elements, features or limitations of the presently claimed invention.

As explained above and during the interview, the present invention relates to methods of treating a neoplasia in a mammal involving administering to the mammal a serum-stable nucleic acid-lipid particle comprising a nucleic acid portion that is fully encapsulated within the lipid portion.

1. Rejection of claim s 1-4, 8, 10-12, 16-18, 23, 28, 42, 44, and 46 under 35 U.S.C. § 102(e) over Kirn *et al.*

Kirn *et al.* was initially cited as teaching methods of treating neoplasia in a mammal comprising the administration of a serum-stable, nucleic acid-lipid particle comprising a fully encapsulated nucleic acid encoding a therapeutic proto-oncogenic polynucleotide.

Applicants noted for the Examiner that the presently claimed methods comprise administering lipid-nucleic acids particles in which the nucleic acids are *fully encapsulated* within the lipid-nucleic acid particles. Since the nucleic acids of the lipid-nucleic acid particles of the present invention are fully encapsulated, degradation of the

nucleic acids by nucleases is greatly reduced. As explained by the Applicants, the lipid-nucleic acid particles disclosed in Kirn *et al.* are lipoplexes of lipid and nucleic acid, *i.e.*, complexes of lipids with nucleic acids in which the nucleic acids are ***not*** encapsulated. Thus, in contrast to the presently claimed invention, Kirn *et al.* do not teach nucleic acids *fully encapsulated* within lipid-nucleic acid particle. During the telephonic interview of February 25, 2003, the Examiner agreed that administration of the lipid and nucleic acid complexes described by Kirn *et al.* does not anticipate the presently claimed methods of treating neoplasia by administering lipid-nucleic acids particles in which the nucleic acids are *fully encapsulated* within the lipid-nucleic acid particles.

Thus, Kirn *et al.* fail to disclose all of the elements of the claimed invention, *i.e.*, methods of treating neoplasia in a mammal comprising the administration of a serum-stable, nucleic acid-lipid particle comprising a fully encapsulated nucleic acid and does not anticipate the claimed invention. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §102(e) be withdrawn.

2. Rejection of claims 1-4, 8, 10-12, 16-18, 23, 28, 39-42, 44, and 46 under 35 U.S.C. § 102(e) over Hung *et al.*

Hung *et al.* was initially cited as teaching methods of treating neoplasia in a mammal comprising the administration of a serum-stable, nucleic acid-lipid particle comprising a fully encapsulated nucleic acid encoding a therapeutic proto-oncogenic polynucleotide.

Applicants noted for the Examiner that the presently claimed methods comprise administering lipid-nucleic acids particles in which the nucleic acids are *fully encapsulated* within the lipid-nucleic acid particles. Since the nucleic acids of the lipid-nucleic acid particles of the present invention are fully encapsulated, degradation of the nucleic acids by nucleases is greatly reduced. As explained by the Applicants, the lipid-nucleic acid particles disclosed in Hung *et al.* are lipoplexes of lipid and nucleic acid, *i.e.*, complexes of lipids with nucleic acids in which the nucleic acids are ***not*** encapsulated. Thus, in contrast to the presently claimed invention, Hung *et al.* do not teach nucleic acids *fully encapsulated* within lipid-nucleic acid particle. During the telephonic

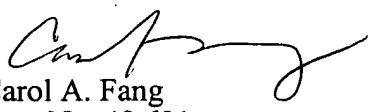
interview of February 25, 2003, the Examiner agreed that administration of the lipid and nucleic acid complexes described by Hung *et al.* does not anticipate the presently claimed methods of treating neoplasia by administering lipid-nucleic acids particles in which the nucleic acids are *fully encapsulated* within the lipid-nucleic acid particles.

Thus, Hung *et al.* fail to disclose all of the elements of the claimed invention, *i.e.*, methods of treating neoplasia in a mammal comprising the administration of a serum-stable, nucleic acid-lipid particle comprising a fully encapsulated nucleic acid and does not anticipate the claimed invention. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §102(e) be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, the Examiner is invited to call the undersigned at 415-576-0200.

Respectfully submitted,



Carol A. Fang
Reg. No. 48,631

TOWNSEND and TOWNSEND and CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
Tel: (415) 576-0200
Fax: (415) 576-0300
CAF:jmm
SF 1395547 v1

APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES MADE

4. (Once amended) A method of treating a neoplasia in a mammal in accordance with claim 2, wherein said gene is [exogenous] heterologous.

6. (Once amended) A method of treating a neoplasia in a mammal in accordance with claim 2, wherein said gene encodes a member selected from the group consisting of herpes simplex virus thymidine kinase (HSV-TK), cytosine deaminase, xanthine-guaninephosphoribosyl transferase, purine nucleoside phosphorylase, cytochrome P450 2B1[and analogs thereof]

47. (New) A method of treating a neoplasia in a mammal, said method comprising administering to said mammal a serum-stable nucleic acid-lipid particle comprising a nucleic acid portion that is fully encapsulated within the lipid portion,

wherein said administration is by injection at an injection site that is distal to said neoplasia in said mammal; and

wherein said neoplasia is responsive to the gene product of the nucleic acid.

48. (New) A method of treating a neoplasia in a mammal, said method comprising administering to said mammal a serum-stable nucleic acid-lipid particle comprising a nucleic acid portion that is fully encapsulated within the lipid portion,

wherein said administration is by injection at an injection site that is distal to said neoplasia in said mammal; and

wherein cells of said neoplasia are transfectable by said nucleic acid-lipid particle.

49. (New) The method of claim 47, wherein said nucleic acid encodes a member selected from the group consisting of: suicide enzymes, toxins, tumor suppressor genes, and cytokines.

50. (New) The method of claim 47, wherein said nucleic acid encodes a suicide enzyme.

51. (New) The method of claim 47, wherein said nucleic acid encodes a toxin.

52. (New) The method of claim 47, wherein said nucleic acid encodes a tumor suppressor protein.

53. (New) The method of claim 47, wherein said nucleic acid encodes a cytokine.

54. (New) The method of claim 50, wherein the suicide enzyme is a member selected from the group consisting of: HSV-TK, purine nucleoside phosphorylase, and cytosine deaminase.

55. (New) The method of claim 50, wherein the neoplasia is melanoma.

56. (New) The method of claim 50, wherein the neoplasia is colorectal cancer.

57. (New) The method of claim 50, wherein the neoplasia is sarcoma.

58. (New) The method of claim 51, wherein the toxin is *Pseudomonas* exotoxin.

59. (New) The method of claim 51, wherein the tumor suppressor protein is apoptin.

60. (New) The method of claim 51, wherein the cytokine is IL-12.

61. (New) The method of claim 51, wherein administration of the serum-stable nucleic acid-lipid particle is intravenous.